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EFFECTS OF DROPERIDOL ON ACTIVITY OF CAROTID BODY CHEMORECEPTORS IN CAT

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1 The effect of droperidol on the spontaneous activity of carotid body chemoreceptors and on their response to various stimuli was studied in 21 anaesthetized, paralyzed and artificially ventilated cats. Carotid body blood flow was controlled with a perfusion pump, and drugs were injected into the perfusion circuit.

2 In low doses, droperidol transiently increased the rate of spontaneous chemoreceptor activity, but in higher doses it depressed chemoreceptor activity after an initial stimulation.

3 Droperidol reduced or abolished the normal increase in chemoreceptor activity produced by stagnant asphyxia. This effect did not depend solely on the ability of droperidol to suppress spontaneously occurring impulses. Chemoreceptor responses to sodium cyanide, and to dopamine were also inhibited.

4 Dopamine antagonists other than droperidol were also studied for their effect on chemoreceptor activity. Chlorpromazine depressed spontaneous chemoreceptor activity and also reduced the chemoreceptor responses to sodium cyanide and dopamine, as did pimozide. The effects of these dopamine antagonists were much briefer and less marked than those of droperidol.

5 Although the influence that we have shown droperidol to have on peripheral chemoreceptor activity has an uncertain basis, it may have important implications in human and veterinary medicine.

Introduction

Droperidol is a neuroleptic agent with properties of an α-adrenoceptor antagonist (Yelnosky, Katz & Dietrich, 1964). In recent years it has been used with increasing frequency in combination with a narcotic analgesic, usually fentanyl, for analgesic, tranquillizing and anaesthetic purposes (Zauder & Nichols, 1969). Among the most common, serious adverse reactions to this combination of drugs are respiratory depression and apnoea. These complications have been attributed to fentanyl, which decreases the ventilatory responses to carbon dioxide (Kallos & Smith, 1969) and produces rigidity of respiratory muscles (Zauder & Nichols, 1969). Droperidol itself reportedly has no central respiratory depressant effects, although it may intensify or prolong those of anaesthetics such as pentobarbitone (Kissil & Yelnosky, 1968). It has been suggested that this potentiation of anaesthetic-induced respiratory depression is due either to interference by droperidol with the metabolism of barbiturates, or to a reduction in the effects of afferent impulses on the non-specific reticular activating system (Kissil & Yelnosky, 1968). However, another possible mechanism is that droperidol reduces the frequency of impulses in afferent fibres arising from peripheral chemoreceptors, and thus impairs the primary drive to ventilation during drug-induced central respiratory depression.

Little is known about the effects of droperidol on peripheral chemoreceptors. In previous work on the carotid body of cats, we found that small doses of droperidol reduced or abolished the inhibitory effects produced on chemoreceptors by exogenously administered dopamine or by increased centrifugal activity due to electrical stimulation of the same carotid sinus nerve (Sampson, Aminoff, Jaffe & Vidruk, 1976a). In the present study we have examined the effects of droperidol on spontaneous activity of carotid body chemoreceptors of the cat and on the responses of these chemoreceptors to various stimuli. We have also compared the effects of droperidol with those of certain other dopamine antagonists.

Methods

Experiments were performed on 21 cats (2.1–4.2 kg) anaesthetized with intraperitoneal sodium pentobarbitone (Diabutal, Diamond Labs., Inc.), 36 mg/kg,

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paralyzed with intravenous gallamine triethiodide (Flaxedil, American Cyanamid Co.) 6 mg/kg, and ventilated artificially. Anaesthesia was supplemented with intravenous pentobarbitone (5 mg/kg) as required. Femoral artery pressure was measured with a Statham transducer (P 23Gb), and end-expiratory P_{CO_2} was measured with a Beckman LB-1 infrared analyzer, both being recorded on a Grass polygraph.

The region of the carotid sinus and carotid body was exposed by a midline incision in the neck, the trachea and oesophagus being transected and reflected cranially. The right carotid sinus nerve was cut close to its junction with the glossopharyngeal nerve and separated from surrounding tissue along its length to as close to the carotid body as possible. The freed end rested on a stainless steel platform, and fine strands were dissected under warm (35–37°C) liquid paraffin. Impulses in single or few fibre strands of chemoreceptor afferent fibres were recorded with platinum electrodes, amplified and displayed on an oscilloscope. The vertical signal output from this oscilloscope was fed to an audiomonitor, pulse-height selector, ratemeter, and to a second oscilloscope from which photographs were made on moving film. The analog output of the ratemeter was recorded on the polygraph and provided a continuous record of the impulse frequency in chemoreceptor fibres. The ratemeter was equipped with a divider circuit which provided recurrent pulses for a predetermined number of impulses, and the pulse output of this circuit was also recorded on the polygraph. The digital output of the ratemeter was fed to a frequency meter (Faratron) so that the total number of impulses counted in any pre-selected period of time could be determined.

The blood supply to the carotid body was isolated and controlled with a perfusion pump interposed in an extracorporeal circuit (internal volume = 1 ml), so that in some experiments chemoreceptor activity could be stimulated by stagnant asphyxia (McCloskey & Black, 1971; Sampson, Aminoff, Jaffe & Vidruk, 1976b). The input of the pump was connected to the cardiac end of the common carotid artery, and a catheter from the output of the pump was inserted into the central end of the common carotid artery, immediately caudal to the carotid sinus. Blood flow through the carotid body could thus be stopped at will by turning off the pump, occluding the occipital artery distal to the carotid body and opening the perfusion circuit to atmospheric pressure via a valve. A short section of thick-walled silicone tubing, into which bolus injections could be made, was placed on the cardiac side of the circuit. Carotid sinus pressure was measured by a catheter inserted into it via the lingual artery and connected to a transducer whose output was recorded on the polygraph. Carotid sinus pressure was normally maintained within 20 mmHg of the femoral artery pressure by adjusting the speed of the pump, and fell to 0 mmHg when flow through the carotid body was stopped.

The following drugs were administered to the carotid body by injection into the perfusion circuit in the doses indicated: dopamine (Calbiochem.), 2–25 μg; sodium cyanide (NaCN; UC Hospital Pharmacy) 1–10 μg; droperidol (McNeil Labs, Inc.) 10–450 μg; chlorpromazine (McNeil Labs, Inc.) 10–600 μg; pimozide (McNeil Labs, Inc.) 50–500 μg. With the exception of pimozide, the drugs were prepared freshly in 0.9% w/v NaCl solution (saline) for each experiment and the concentrations adjusted so that the desired dose was contained in a volume less than 0.05 ml. In the case of pimozide, 10 mg of it and 60 mg of tartaric acid were dissolved in 4 ml distilled water. The time taken for drugs to reach the carotid body after injection into the circuit was determined in each experiment after the pump speed had been set, and varied between 14 and 27 s in the different experiments. This was accomplished by injecting a test dose of 5 μg NaCN and noting the latent period before an increase in chemoreceptor activity occurred.

Results

Fibres were identified as arising from chemoreceptors in the carotid body (a) by the occurrence of an increase in their discharge frequency when flow through the carotid body was reduced or abolished, and a decrease in activity upon its restoration, and (b) by their responses to NaCN (see Methods).

Spontaneous chemoreceptor activity

The effect of droperidol on the spontaneous rate of discharge of chemoreceptors was studied in 39 tests on 19 single or few fibre preparations. The responses obtained appeared to be dose-related, at least in part, as shown in Figure 1. In doses of 10–25 μg (5 tests on 4 fibres), droperidol caused the rate of discharge to increase transiently. The duration of this increase varied between 20 s and 14 min in different preparations, and following it, activity returned to control levels. With doses ranging between 50 and 100 μg, chemoreceptor activity was again stimulated, but this was followed by depression of activity in 4 of 7 fibres tested. The degree of depression ranged from 22% for 2.5 min to complete suppression of activity for 6 minutes. As the dose of droperidol was increased above 100 μg, the initial phase of chemoreceptor stimulation became briefer and less impressive, while depression of activity became longer and more intense than with the low doses. Thus, stimulation followed by depression occurred in 8 of the 10 chemoreceptor fibres tested with 200–250 μg droperidol. This pattern (i.e.,

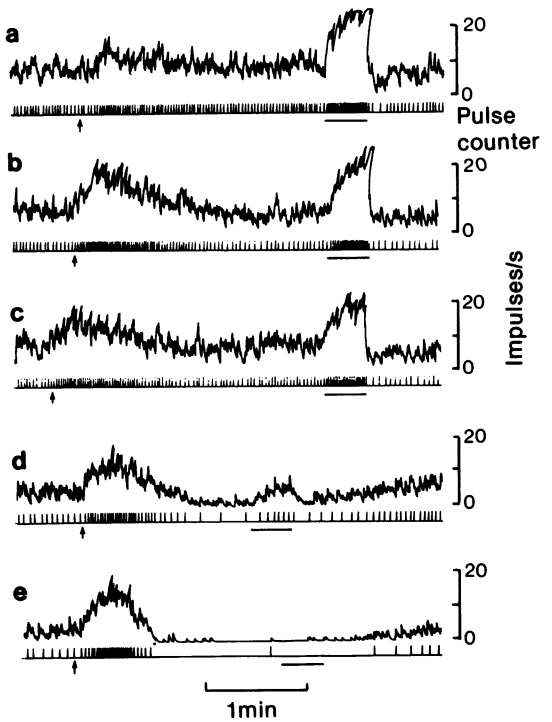

Figure 1 Effects of increasing doses of droperidol on spontaneous activity and on the response to stagnant asphyxia of a single chemoreceptor fibre. Records (a) to (e) show the responses to doses of 20, 50, 100, 250 and 300 μg of droperidol, respectively, the drug being given at the time indicated by the arrow in each case. The horizontal bar in each record denotes a 30 s period during which blood flow through the carotid body was stopped. In each record, the upper trace is the analog output of the ratemeter (impulses/s), and the lower trace is the pulse output (20 impulses/pulse). The time allowed to elapse between each injection of droperidol ranged from 21–27 minutes.

stimulation followed by depression) was not due to a cumulative effect of droperidol, as in 5 of the 8 fibres this was the first dose given. The amount of stimulation ranged from 25% to 400%, and its duration from 20 to 125 seconds. In contrast, activity was depressed for as long as 11.5 min and during this time the activity was often completely suppressed. Of the remaining 2 fibres, the activity of one was depressed by 30% for 1.5 min and that of the other was not depressed at all by droperidol (325 μg). Still higher doses of droperidol caused an even greater inhibition of chemoreceptor activity, lasting 5–16 min in 6 of 8 fibres tested.

The pattern of an increase, followed by a decrease, in chemoreceptor activity also occurred in each of 3 additional fibres in different animals when droperidol was administered intravenously (1–2 mg/kg) rather than into the perfusion circuit.

Chlorpromazine was studied for its effect on 8 chemoreceptor fibres in 5 cats. In doses ranging between 50 and 300 μg and injected into the perfusion circuit, it had a mild stimulant effect on spontaneous chemoreceptor activity (4 of 6 tests on 3 fibres). In higher doses (400–600 μg), spontaneous activity was depressed for 30–190 s in 3 of 7 tests on 5 fibres. Injections of pimozide in doses of 20–500 μg always increased chemoreceptor activity (5 chemoreceptor fibres in 4 experiments). This effect also occurred on injection of the diluent (tartaric acid) for pimozide and could not, therefore, be attributed to the drug itself. In no case did pimozide depress spontaneous chemoreceptor activity.

Chemoreceptor responses to stagnant asphyxia

When blood blow through the carotid body is arrested, the resultant stagnant asphyxia increases the frequency of discharges in chemoreceptor fibres (McCloskey & Black, 1971; Sampson, Aminoff, Jaffe & Vidruk, 1976b). We examined the effect of droperidol on this chemoreceptor response in 21 tests on 11 fibres. In order to take into consideration any changes in spontaneous activity that may have occurred with time, we calculated the ratio of the number of impulses in the 30 s period during which flow was stopped to the number of impulses in the 30 s period immediately before flow was stopped, and compared the ratios obtained before and after administration of droperidol. For the control studies, an equal volume of the diluent for droperidol was injected into the circuit before stopping the flow.

In 17 of 21 tests, droperidol (10–325 μg) reduced or abolished the increase in chemoreceptor discharge caused by cessation of blood flow. However, there was some variability in the responses obtained from the different preparations. Thus, in one preparation 10 μg of droperidol markedly reduced the response to stagnant asphyxia, whereas in others, doses of 100–250 μg were without effect. Nonetheless, the effects of droperidol were dose-related, as shown in Figure 1. Doses of 100–200 μg reduced or abolished the responses to cessation of flow in 6 of 8 tests (6 fibres), and doses of 250–325 μg did so in 9 of 10 tests (6 fibres).

An example of this depressant effect of droperidol on the chemoreceptor response to stagnant asphyxia is shown in Figure 2. In general, responses were noticeably depressed for at least 5–6 min and did not return to control values until about 10 min or longer after droperidol had been given. Whenever droperidol

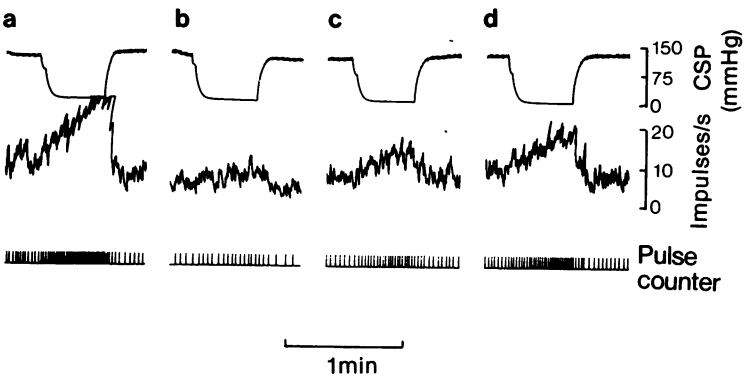

Figure 2 Effects of droperidol on chemoreceptor responses to stagnant asphyxia. In each record the tracings represent, from above down, carotid sinus pressure (CSP, mmHg), ratemeter output (impulses/s) and pulse counter (20 impulses/pulse). (a) Control response; (b) 2 min after droperidol (200 μg); (c) 4 min after droperidol; (d) 6 min after droperidol.

caused a marked depression of spontaneous activity, chemoreceptor responses to stagnant asphyxia were also reduced or abolished. However, responses to stagnant asphyxia were also reduced or abolished in 6 tests on 7 fibres whose rate of spontaneous discharge was not at all depressed by droperidol. Thus, the depressant effect of droperidol on chemoreceptor responses to stagnant asphyxia did not depend solely on its ability to suppress spontaneously occurring impulses. Chlorpromazine and pimozide were not tested for their effects on chemoreceptor responses to stagnant asphyxia.

Responses to NaCN

The effect of droperidol (10–450 μg) on responses of chemoreceptors to NaCN (1–10 μg) was examined in 9 tests on 7 fibres, and the increase in discharge produced by NaCN was either abolished (Figure 3a, b) or reduced (Figure 3c, d) in 8 of these. This effect was observed in 5 fibres whose responses to stagnant asphyxia had also been reduced by droperidol and in 2 whose responses had not. The effect of droperidol lasted for different periods of time in the different preparations.

Chlorpromazine in doses of 400–600 μg also reduced or abolished chemoreceptor responses to NaCN, but lower doses were ineffective in this respect. Similarly, pimozide interfered with chemoreceptor response to NaCN in doses of 250–500 μg but not in lower doses.

Responses to dopamine

Dopamine is known to inhibit spontaneous chemoreceptor activity in cats (Black, Comroe & Jacobs, 1972; Sampson, 1972). In every preparation in which it was tested (17 single or few fibre preparations; 13 cats), droperidol (10–25 μg) abolished the inhibitory response of the carotid body to dopamine in doses of 2–25 μg via the perfusion circuit. This effect persisted for the duration of the remainder of the experiment (up to 7 hours). Chlorpromazine (50–300 μg) consistently reduced or abolished the inhibitory effect of dopamine, but it returned within a few minutes (13 min at the most) in every case. Pimozide (50–100 μg) also reversibly blocked inhibition of chemoreceptor activity by dopamine, the blockade lasting for 30–180 min at the higher doses.

Discussion

The results obtained in the present study clearly indicate that droperidol alters both the spontaneous activity of carotid body chemoreceptors, and their responses to various stimuli. Thus, droperidol caused a transient increase in rate of chemoreceptor activity in most of the fibres tested, and this was followed in many by a relatively longer-lasting depression of activity. In addition, the inhibitory effects of dopamine were markedly reduced or abolished by droperidol.

Pimozide and chlorpromazine also depressed carotid body chemoreceptors, but their effects in this regard were clearly less powerful than those of droperidol. Thus, high doses of chlorpromazine eliminated spontaneous chemoreceptor activity for less than 1.5 min, and pimozide failed to do so at all, whereas droperidol completely or markedly depressed activity for very much longer. Similarly, droperidol frequently abolished the responses of chemoreceptors to various

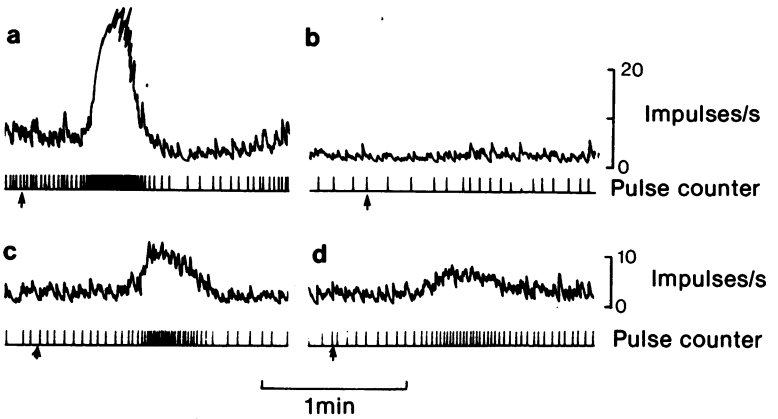

Figure 3 Effects of droperidol on chemoreceptor responses to NaCN. Tracings as in Figure 1. The pulse counter tracing displays a pulse for every 10 impulses in (a) and (b), and a pulse for every 20 impulses in (c) and (d). In each case, NaCN was injected at the time indicated by the arrow. (a) Control response to 5 μg NaCN; (b) response obtained 4 min after administration of droperidol (250 μg) showing little, if any, effect of NaCN; (c) control response to 1 μg NaCN in another preparation; (d) reduced response to NaCN obtained 7 min after administration of droperidol (200 μg).

stimulants, whereas chlorpromazine and pimozide, even in the highest doses we used, merely reduced them.

Droperidol, like other butyrophenones such as haloperidol (see Jansen, 1967), is a competitive antagonist of dopamine, noradrenaline and adrenaline on α-adrenoceptors (Yelnosky *et al.*, 1964). Other α-adrenoceptor antagonists, such as phenoxybenzamine and dihydroergotamine, also cause an increase in spontaneous chemoreceptor activity (Sampson, 1972; Sampson *et al.*, 1976a), but this is of longer duration than that occurring with droperidol, and is not followed by depression. There is evidence to suggest that centrifugal impulse traffic in the carotid sinus nerve has a tonic inhibitory effect on chemoreceptor activity, and that this effect is mediated through the release of endogenous catecholamines (Sampson *et al.*, 1975). The initial increase in chemoreceptor activity which we found to occur following administration of droperidol may, therefore, have been secondary to its action as an α-adrenoceptor antagonist, provided that catecholamines are released spontaneously from their storage sites in the carotid body. The blockade by droperidol of the inhibition of chemoreceptor activity normally caused by exogenous dopamine, or by stimulation of the carotid sinus nerve (Sampson *et al.*, 1976a) is probably due to its ability to block α-adrenoceptors, or specific dopamine receptors.

The secondary suppression of spontaneous chemoreceptor activity which followed administration of droperidol, and the reduction which the latter caused in the chemoreceptor responses to stagnant asphyxia and to NaCN, cannot be explained by α-adrenoceptor blockade. One possible explanation is that these depressant effects of droperidol are due to local anaesthetic actions. In support of this view are the observations of Hauswirth (1968), who found that droperidol reduced both the duration and rate of rise of the action potential of Purkinje fibres in sheep, resulting in inexcitability. Hauswirth tentatively attributed this phenomenon to blockade of the sodium-carrying system and concluded that droperidol had 'stabilized' the cell membrane, although he was unable to determine whether this occurred in a manner similar to local anaesthetics and quinidine, or to tetrodotoxin. Hence, suppression of chemoreceptor responses by droperidol could have been due to a non-specific stabilizing effect on the cell membrane. Further experimental work is necessary to validate this point.

A second possibility is that the depressant effects of droperidol were secondary to changes in blood flow. Puddy (1971) suggested that droperidol is a non-specific inhibitor of vasoconstriction in the isolated auricular artery of the rabbit, because it antagonizes vasoconstriction induced by histamine or potassium ions, as well as that produced by noradrenaline or stimulation of the sympathetic nerves. Chemoreceptor activity is influenced by blood flow through the carotid body, presumably because the latter alters the chemical environment of the receptor. Blockade of vasoconstriction, and the resultant increase in flow to which it leads, could theoretically account for the depression caused by droperidol in spontaneous activity of chemoreceptors and in their responses to

NaCN. The blockade of the response to stagnant asphyxia by droperidol could also be explained on this basis, if it is assumed that the increase in flow prior to the asphyxia protected the chemoreceptors from the effects of the latter in a manner similar to that suggested by McCloskey & Black (1971) to account for the effects of hyperoxia.

Our observations that droperidol diminishes the responsiveness of chemoreceptors in cats, raise the possibility that it also does so in human beings, despite species differences. In such circumstances, certain important implications would follow with regard to human and veterinary medicine. Droperidol is frequently given to patients in combination with a narcotic analgesic, usually fentanyl. The latter depresses respiration (Gardocki & Yelnosky, 1964) by interfering with central responses to CO_2 (Dunbar, Ovassapian, Dripps & Smith, 1967), so that the peripheral chemoreceptor drive to respiration would assume particular importance in maintaining respiration. We have shown that droperidol can depress the responsiveness of peripheral chemoreceptors to stagnant asphyxia, and the resultant failure of this drive to ventilation could be life-threatening.

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